ORIGINAL ARTICLE

CURCUMA LONGA RENAL HISTORESTORATIVE EFFECTS ON SILDENAFIL INDUCED NEPHROTOXICITY AMONG MALE ALBINO RATS.

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ABSTRACT

Background: Sildenafil is a phosphodiesterase type 5 inhibitor mostly used in management of erectile dysfunction and pulmonary hypertension. On the other hand, Curcuma longa is herbal plant that is mostly used in diets among the Asian and African population and commonly used in treatment of respiratory, renal and dermatological diseases. Methods: A post-test only true experimental study design was utilized with 25 Albino rats grouped as follows: negative control, positive control (sildenafil 1µg/g bwt), low dose Curcuma longa (38.75mg/kg), medium dose Curcuma longa (77.5mg/kg) and high dose Curcuma longa (155mg/kg) each having 5 rats. Induction of nephrotoxicity using sildenafil was done for 15 days with an interim sacrifice for negative and positive control groups done on day 15. Experimental groups were sacrificed on day 22 after receiving Curcuma longa at respective doses. Blood samples for renal function tests were obtained on day 1, 15 and 22. Enblock harvesting of the kidneys after euthanizing the rats with concentrated CO₂ and 10% neutral buffered formalin perfusion was done on day 15 and 22 then fixed in 10% neutral buffered formalin for 24hours. The kidneys were then processed for Hematoxylin and Eosin staining and photomicrographs were taken using Olympus light microscope fitted with LABOMED ivu 3100 digital camera. Results: In sildenafil induced nephrotoxicity group; glomerulus was distorted, dil ated bowman`s space, dilated renal tubules and necrotic epithelial cells. Minimal histological changes were observed in low Curcuma longa dose group while in medium and high Curcuma longa dose groups; the glomerulus had well defined margins, bowman`s space reduced in size, epithelial cells appeared normal. Conclusion: It can be concluded that medium and high dose Curcuma longa have kidney historestorative effects in sildenafil induced nephrotoxicity among male albino rats.

Keywords: Curcuma longa, Historestorative, Kidney, Nephrotoxicity and Sildenafil.
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INTRODUCTION

Nephrotoxicity is kidney rapid deterioration function due to toxic effect of medicines, chemicals, environmental and industrial toxins (Lv & Zhang, 2019) . Drug induced nephrotoxicity is the third leading cause of acute kidney injury as this type of nephrotoxicity has a wide range of damage on the nephron (Sales & Foresto, 2020). Sildenafil has wide variant methods of nephrotoxicity as it affects different parts of kidney namely; glomerulus, bow man capsule, medulla, cortex, medullary tubule, cortical tubules, proximal convoluted tubule, renal vessels and glomerular capillaries. It releases oxidative chemicals that can cause stress thereby damaging cell membrane (Cadirci et al., 2011; Ebrahim et al., 2009) . It causes accumulation of lactate in kidney tubules causing damage to cytoplasm leading to elevation in osmotic pressure that cause water intracellular influx (Medeiros et al., 2017) . The accumulation of calcium
leads to glomeruli calcification and reduced renal function (Küçük et al., 2012). *Curcuma longa* has the physiological properties that can counteract, attenuate, improve and protect the kidney from drug induced nephrotoxicity (Manikandan et al., 2011; Tirkey et al., 2005; Trujillo et al., 2013). However, there is less data which shows the restorative effects of *Curcuma longa* on sildenafil induced nephrotoxicity. *Curcuma longa* is greatly able to protect the kidney from sildenafil induced nephrotoxicity by counteracting the tubular damages, apoptosis and oxidative stress released (He et al., 2015), activities of heme oxygenase, endothelial nitric oxide synthase and gene expression of tumor necrosis factor alpha (Hassan et al., 2019) and it has Curcumin that has anti-inflammatory and antioxidative effects thus able to counteract the reactive oxygen and nitric oxide radicals released (Ueki et al., 2013). Therefore, the aim of this study was to evaluate *Curcuma longa* renal historestorative effects on sildenafil induced nephrotoxicity among male albino rat.

**MATERIALS AND METHODS**

**Experimental animals**
A total of twenty-five male albino of species *Rattus norvegicus* rats were used. They were simple randomly assigned into five groups as either; control, sildenafil induced nephrotoxicity, low, medium and high dose *Curcuma longa* groups. The standard experimental conditions like humidity, temperature and light/dark cycle of 12 hours were maintained. Feeds and water were given under strict hygiene conditions with researcher upholding occupational animal handling procedures.

**Drug administration**
The four subgroups received a single dose of 1µgm/gm bwt/day sildenafil(Suriyakumari et al., 2016) for 15 days through gastric gavage. The five animals in group2 were sacrificed four hours post last dosage and renal function test was done to confirm toxicity while group 3, 4 and 5 were subjected to *Curcuma longa* at 38.75mg/kg, 77.5mg/kg and 155mg/kg respectively for seven days to try and restore the damage that had been caused(Fança-Berthon et al., 2021; Nair & Jacob, 2016). Thereafter, renal function test was done to confirm if restoration had been effective.

**Sacrificing and histological preparation**
CO₂ was used as anesthesia after which a vertical incision was made from pubic symphysis to xiphoid process so as to expose the viscera and collect the kidneys. The kidneys were identified and excised. The fibrous capsule and adipose tissue were removed. They were then preserved in 10% formalin. Later, they were stained using hematoxylin and eosin stains and observed under a light microscope. Photomicrographs were then taken and key histological changes were noted and described as below. The ethical approval to carry out the study was sought from Baraton University of Eastern Africa (UEAB/ISERC/08/01/2023) and NACOSTI (NACOSTI/P/2023/23374).

**RESULTS**

**Histological findings in negative control group and sildenafil induced nephrotoxicity group.**
In negative control group (feeds + water ad libitum), the glomerulus was surrounded by a narrow bowman`s space. The epithelial cells were normal along the proximal tubule with well-defined margins and lumen had normal brush borders. In sildenafil induced nephrotoxicity group, the glomerulus was distorted with a dilated bowman`s space, dilated cortical tubule with deranged
borders, vacuolations, necrotic epithelial cells and lumen had distorted brush borders (Figure 1). Kidney histo-morphological findings among low, medium and high Curcuma longa groups. 

In low Curcuma longa dose (38.75mg/kg/day), the glomerulus had poor defined margins and was surrounded by a bowman`s space. The epithelial cells appeared cuboidal in shape around the cortical tubule while the lumen had defined borders. In medium Curcuma longa dose (77.5mg/kg/day), glomerulus had poor defined margins, narrow bowman`s space, the lumen was well defined (Figure 2). In high Curcuma longa dose (155mg/kg/day), the glomerulus had well defined margins and a narrow bowman`s space, the epithelial cells appeared cuboidal and the lumen had well defined brush borders (Figure 3).

Figure 1: Photomicrograph A, control showing normal glomerulus, normal epithelial cells, bowman`s capsule and proximal convoluted tubule. B, in Sildenafil induced nephrotoxicity showing distorted glomerulus, dilated bowman`s capsule and cortical tubule with necrosis. At x10 using hematoxylin and eosin stain. G=glomerulus, PCT=proximal convoluted tubule, BC=bowman`s capsule, A=control group and B= sildenafil induced nephrotoxicity group.

Figure 2: Photomicrograph C, low Curcuma longa dose showing glomerulus with defined margins, cuboidal epithelial cells, bowman`s capsule and proximal convoluted tubule with defined edges. D, in medium Curcuma longa dose
showing normal glomerulus with well-defined margins. At x10 using hematoxylin and eosin stain. G=glomerulus, PCT=proximal convoluted tubule, BC=bowman`s capsule, EC= epithelial cells, C=low Curcuma longa dose group and D= medium Curcuma longa dose group.

Figure 3: Photomicrograph E and F high Curcuma longa dose showing normal glomerulus with well-defined margins, narrow bowman`s capsule and cortical tubule normal epithelial cells. At x10 using hematoxylin and eosin stain. G=glomerulus, PCT=proximal convoluted tubule, BC=bowman`s capsule, EC= epithelial cells, E and F=high Curcuma longa dose group.

DISCUSSION

In the current study, it was observed that sildenafil caused gross glomerular damage and widening of bowman`s space which was mediated by cellular degeneration and necrosis (Figure 1 B). This observation is in agreement with the results reported by (Mohammed & Khudair, 2020) who observed similar changes when diclofenac was used in induction of Acute kidney injury. There was obvious distortion, shrinkage of the glomerulus and glomerulosclerosis (Figure1B) on microscopic study in concurrence with the findings of (Ali et al., 2018). This progressive morphological changes in histoarchitecture of kidney may be due to decrease in glomerular filtration of the drug as a result of capillary constriction and increased pro-inflammatory cytokines which lead to a primary renal injury (Suriyakumari et al., 2016). There were vacuolations seen in the current study (Figure1B) which was mediated by increase in production of lactate that accumulates within the cytoplasm and potentially leading to cellular membrane damage as noted in previous studies (Suriyakumari et al., 2016). There was damage and necrosis of epithelial cells and massive dilatation of proximal tubules and distorted lumen. Previous studies observed that these changes might have been modulated by infiltration of inflammatory cells, intensive swelling of epithelial cells when exposed to oxidant stress which leads to increased production of nitric oxide that reacts with free radicals causing renal damages (Kirbas et al., 2015).

In the current study, there was improvement in the general structure of epithelial cells, the proximal convoluted tubule had defined margins with a narrow lumen as seen (Figure 3 & 4) as compared to positive control group. This general improvement in epithelial cells and proximal convoluted tubules may be due to prevention of renal tubular and epithelial cell degeneration and presence of curcumin in Curcuma longa that restores tubular brush borders and anatomical efficiency of renal
tubular basement membrane (Ahmad et al., 2020; Liu et al., 2017).

On observation, the current study noted that the glomerulus was histomorphologically restored with well-defined margins after administration of Curcuma longa (Figure 3 & 4) as compared to positive control group (Figure 3 & 4). (Ahmed et al., 2015) reported a similar result on kidney histomorphology after assessing the effects of Curcumin and garlic on methotrexate and carbon tetrachloride induced nephrotoxicity, they noted a complete histomorphological restoration of glomeruli and its surrounding margins. This markable improvement in restructuring of the glomerulus may have been due to reduced infiltration of inflammatory cells and release of inflammatory markers that prevent necrosis from taking place. Curcumin being an active component in Curcuma longa has the ability to restore the glomerular capillaries to normal size thus improving glomerular filtration rate of glomerulus (Russo et al., 2018).

CONCLUSION
Based on this study, it can be concluded that medium and high dose Curcuma longa have historestorative benefits on sildenafil induced nephrotoxicity among male albino rats. Therefore, Curcuma longa can be used in the management or can be considered as a component in formulating drugs that can be used in treatment of sildenafil induced nephrotoxicity.

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REFERENCES


